Development and Validation of a New Scoring System for the Early Diagnosis of Tuberculous Meningitis in Adults

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Research article

Keywords: Central nervous system infections, Tuberculous meningitis, Diagnostic scoring system, HIV negative adults

DOI: https://doi.org/10.21203/rs.3.rs-31333/v1

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Abstract

Background

The absence of a sufficiently accurate and efficient diagnosis of tuberculous meningitis (TBM) is major obstacle to delayed treatment, and its non-specific clinical manifestations easily mimic the central nervous system infections caused by other causes, including virus, bacteria, and cryptococcus. This study aims to develop and validate a diagnostic score system for TBM in HIV-uninfected adults by simultaneously comparing TBM with viral meningitis (VM), bacterial meningitis (BM), and cryptococcal meningitis (CM).

Methods

Twenty-nine factors (including clinical, laboratory and imaging) were assessed among 382 patients who satisfied inclusion criteria for TBM (n = 113), VM (n = 143), BM (n = 65) and CM (n = 61). Independent predictors for the diagnosis of TBM were obtained by logistic regression to establish a diagnostic scoring system. The performance of this scoring system was evaluated using a prospective validation cohort.

Results

Nine factors independently associated with the diagnosis of TBM: symptom duration (10–30 days), systemic symptoms, evidence of extra-central nervous system tuberculosis, cerebrospinal fluid (CSF) leukocyte count (100-500×10^6/mL), CSF neutrophil proportion (20%-75%), CSF protein (> 1 g/L), low serum sodium (< 137 mmol/L), meningeal enhancement, and brain parenchymal nodules (tuberculomas). The CSF neutrophil proportion was assigned a score of 2 and all other factors were assigned a score of 1. A score of at least five was suggestive of TBM with a sensitivity of 85.8% and a specificity of 87.7%, and the area under the receiver operating characteristic curve (AUC) was 0.927. When applied prospectively to an additional 72 patients (21 with TBM, 27 with VM, 14 with BM, and 10 with CM), the sensitivity, specificity, accuracy, and AUC values of this scoring model were 90.5%, 86.3%, 87.5%, and 0.944, respectively.

Conclusions

For differential diagnosis between TBM and other causes of meningitis (VM, CM and BM), we developed and validated a new weighted scoring system. The application of this scoring system can help diagnose TBM more efficiently in the early stage.
Tuberculous meningitis (TBM), as the most severe form of extrapulmonary tuberculosis, constitutes 5%–10% of all extrapulmonary cases[1] and leads to substantial morbidity and mortality in more than 50% of cases, largely due to difficulty in rapid diagnosis and delayed initiation of treatment[2–4]. TBM diagnosis at an early stage is difficult as its presentation is non-specific and rapid, sensitive, and affordable diagnostic tests are often not available, especially in developing countries with a high incidence of tuberculosis and relatively poor diagnostic techniques[5]. Cerebrospinal fluid (CSF) smear has low sensitivity (≤ 15%), and the culture is too slow (6–8 weeks) to yield results[6–9]. Even the sensitivity of Xpert MTB/RIF, which is recommended by WHO for diagnosis of TBM, is relatively low (55%–80%)[10, 11]. The future prospects of the next Xpert MTB/RIF Ultra for the detection of tuberculosis should be further assessed in developing countries. In the absence of a high sensitivity assay that can 'rule out' TBM and given the fatal consequences of delayed diagnosis, the majority of patients will be treated based on compatible clinical features, as well as supportive laboratory and radiological findings. Therefore, easy-to-use diagnostic scores may play a role in distinguishing TBM patients.

Many studies have attempted to establish a diagnostic score for TBM by comparing it with another type of meningitis, such as viral meningitis (VM)[12, 13], bacterial meningitis (BM)[14–17] or cryptococcal meningitis (CM)[18–20]. Most of these studies have varying degrees of sensitivity and specificity, which are related to different TBM definitions and limited samples. A consensus case definition for TBM to help standardize clinical TBM research and make the research directly comparable, but the case definition was not intended to be used as a clinical diagnostic tool[21]. Thus, while these models may accurately predict TBM diagnosis, they vary in their ease of use. There is no standard, widely accepted early diagnostic model for comparison of TBM with other non-TBM, including VM, BM, and CM.

Our study aimed to develop and validate a diagnostic score that can accurately predict TBM at an early stage by simultaneously comparing TBM with the other three clinically common central nervous system (CNS) infections (VM, BM, and CM), attributable to the nonspecific clinical presentation of these four types of CNS infections that may mimic each other. The results may be of certain reference value for improving the diagnostic level of TBM and doctors' understanding, and formulating control plans.

**Methods**

**Patients and materials**

We performed a retrospective study of adult patients (≥ 18 years of age) admitted to the Third Xiangya Hospital of Central South University and Central Hospital of Changsha, Hunan, China with a diagnosis of TBM, BM, VM, and CM from January 2015 to December 2018. The vast majority of patients admitted to the two hospitals come from the southern provinces of China such as Hunan, Jiangxi, Guizhou, Guangxi, and Guangdong.

**Data collection**
We collected information on demographic data (age, gender, place of residence, and occupation), symptom duration (the interval from onset of symptoms to hospital admission), clinical symptoms (meningeal irritation, altered mental status, cranial nerve palsy symptoms, seizure, reduced level consciousness, and others), underlying diseases (such as tuberculosis and HIV infection, diabetes, steroid use, organ transplant, malignancy, renal insufficiency, and other immunosuppressive diseases), laboratory parameters (blood routine, biochemical parameters, erythrocyte sedimentation rate, C-reactive protein, and immunological examination of infectious diseases), CSF analysis results of the first lumbar puncture after admission (routine examination, biochemistry, cytology, microbiology, the modified Ziehl–Neelsen stain, India ink staining, and cryptococcal antigen detection (colloidal gold method, IMMY)), and magnetic resonance imaging (MRI) results of CNS after admission. Specifically, cell count in the CSF was obtained by Neubauer chamber method, cell classification was based on CSF cytology, i.e., fresh CSF was loaded into a cytospin chamber with poly-L-lysine–coated slides and centrifuged at 700 × g for 4–6 minutes, and then Wright-Giemsa stained was used in the obtained sediment.

**Diagnostic criteria**

TBM: CSF positive for acid-fast stain or M. tuberculosis culture, and/or positive GeneXpert MTB/RIF (Cepheid, Sunnyvale, USA).

VM: If a viral etiology was confirmed or the outcome was favorable under supportive or antiviral treatment, and after ruling out bacterial, tuberculous, fungal, and non-infectious causes of meningitis (injury, cancer, autoimmune disorders, neurosarcoidosis).

CM: CSF positive for India ink stain or fungal culture, and/or cryptococcal antigen.

BM: If Pathogenic bacteria isolated from CSF or Clinical meningitis with all of the following: 1) neutrophils dominant in CSF, 2) low concentration of glucose in CSF (< 50% of that in the blood), 3) sterile blood and CSF cultures, 4) full recovery (without anti-tuberculosis chemotherapy) 3 months after admission[16].

**Exclusion criteria**

Patients with any of the following conditions could not participate in the trial: 1) age under 18, 2) data was insufficient, 3) pregnant mothers, 4) patients treated for TBM but were not definite TBM patients, 5) patients with HIV positivity, 6) if they had received more than 7 days of treatment for the current infection, 7) if they have more than two types of microbial infection, or 8) if they underwent a neurosurgical operation during the month before admission.

**Role of the validation cohort**

The diagnostic score was assessed by prospective validation data. Patients included in the validation cohort were diagnosed with VM, BM, CM, and TBM from January 2019 to December 2019. These patients were from multiple hospitals and all underwent CSF cytology in the Laboratory of Neurology of the Third Xiangya Hospital of Central South University. The diagnostic criteria and exclusion criteria were the same.
as those for the study cohort. The clinicians and laboratory technicians involved in making those diagnoses of the validation cohort were blinded to the scoring system. The prediction performance of the model was tested by using this validation data set.

**Statistical analysis**

The clinical, laboratory, and imaging features of patients who fulfilled the diagnostic criteria for TBM and non-TBM (VM, BM, and CM) were compared. For categorical variables, the Chi-square test was used to test the differences between groups, and quantitative features were compared by ANOVA if data accorded with normal distribution, or by Jonckheere-Terpstra test. Variables with P values < 0.05 were entered stepwise into logistic regression analysis by using the forward conditional method. Before introducing them into the logistic regression analysis, the continuous variables were dichotomized by using quartiles and referring to clinical experience. Logistic regression analysis was used to validate the contribution of each attribute to establish our new scoring criteria for TBM diagnosis. The score of each predictor was determined by referring to the odds ratio (OR) value in the logistic regression prediction equation. Receiver operating characteristic (ROC) curves were used to establish the cut-off values to maximize sensitivity while maintaining good specificity. To assess the performance of this scoring system, we computed the sensitivity, specificity, accuracy, and areas under the ROC curves (AUCs) in the validation cohort. Statistical analysis was performed with SPSS version 18.0 (Statistical Package for the Social Sciences Inc, Chicago, IL, USA).

**Results**

**The study cohort**

A total of 382 out of the 976 patients fulfilled the diagnostic criteria for inclusion in this study between January 2015 and December 2018, and they formed the study cohort for data analysis: 113 with TBM, and 143 with VM, 61 with CM, and 65 with BM. All cases of TBM and CM had a definite etiological basis, 31.5% (45/143) of VM cases had CSF PCR confirmation and 33.9% (22/65) of BM cases had bacteriological confirmation. Another 594 patients who did not meet the enrollment requirements were excluded: 225 patients treated for TBM but were not definite TBM patients, 178 patients whose age was under 18, 104 patients had insufficient data, 36 patients were co-infected with HIV, 3 patients were pregnant mothers, 32 patients had received more than 7 days of treatment for the current infection, 12 patients had more than two types of microbial infection, and 4 patients underwent a neurosurgical operation during the month before admission.

In the model study cohort, 29 potential variables were evaluated for model inclusion. The baseline characteristics of the patients are summarized in Table 1 (at the end of the document). Overall, 218/382 (57.1%) were males with ages ranging from 18 to 82 years and a median of 41 years. The analysis of admission variables revealed a set of potentially discriminative variables. Quantitative variables included symptom duration (more than VM and BM but less than CM), CSF leukocyte count and neutrophil proportion as well as protein concentration (higher than VM and CM but lower than BM), serum sodium
and CSF chloride concentrations (lower than VM, BM, and CM); categorical variables included gender, systemic symptoms, history of tuberculosis, cranial nerve palsy, hydrocephalus, meningeal enhancement, brain parenchyma nodule and pre-contrast basal hyperdensity as well as evidence of tuberculosis elsewhere.

The variables were assigned when modeling. To facilitate translation into a clinical rating scale, this part of the data was processed as shown in Additional File1: Table S1. As far as the grouping of patients was concerned, the Non-TBM group was represented by "0" and the TBM group by "1". Continuous variables were dichotomized before incorporation into the logistic regression model. We used symptom duration of 10–30 days, CSF cell count of 100–500*10^6/ml, the proportion of CSF neutrophils of 20%–75%, CSF protein of > 1 g/ L, CSF chloride

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Of all original candidate variables, 9 remained statistically significant in the logistic regression analysis and formed the final set of predictor variables (Table 2). According to the OR of each factor, symptom duration (10-30 days), systemic symptoms, evidence of extra-central nervous system tuberculosis, CSF leukocyte (100-500*10^6/ml), CSF protein (>1g/L), low serum sodium, meningeal enhancement, and brain parenchyma nodules (tuberculoma) were assigned one point. Because the proportion of CSF neutrophils (20%-75%) had the highest OR, it was assigned two points, the maximum weight in the score. Additional score was not assigned for pre-contrast basal hyperdensity, because only a few TBM patients (6.19%) showed this feature, which was not justified based on the strength of outcome association in the logistic regression model.

The diagnostic index for each of the 9 variables is presented in Table 2. The ROC curves of the study cohort for this scoring model are shown in Figure 1. The optimum cutoff value for the total diagnostic index was determined using the ROC curve. Our proposed diagnostic rule was that a score of at least five was suggestive of TBM, with a sensitivity of 85.8% and a specificity of 87.7%, and the AUC value was 0.927 (95%CI, 0.900-0.954; P < 0.001).

The validation cohort

The validation data were recorded from an additional 72 patients: 21 with TBM, 27 with VM, 14 with BM, and 10 with CM. The distribution and indicators of patients in the validation cohort are shown in
Additional File 2: Table S2. ROC curves of the validation cohort are shown in Figure 2. The sensitivity, specificity, accuracy, and AUC values of this scoring model were 90.5%, 86.3%, 87.5% and 0.944 (95%CI, 0.895-0.993; P < 0.001) when the score $\geq$ 5, respectively.

**Discussion**

This study described the early features that distinguish TBM patients and discriminated them from the patients with CNS infection from other causes including virus, bacteria, and cryptococcus. A new diagnostic score of TBM was developed by supplementing early observations, eliminating non-independent predictors, and re-balancing the weight of each indicator, and it validated the score in a prospective population.

TBM mostly manifests as subacute onset[21]. Previous studies have defined the duration of TBM as longer than 5-10 days[12, 14, 15, 17], which did not distinguish TBM from CM. In our study, 66.5% of patients in the TBM group had a symptom duration of 10-30 days. The results suggest that a symptom duration of more than 10 days can help discriminate between TBM and acute meningitis including VM and BM, and a symptom duration of less than 30 days can help differentiate TBM from CM effectively. CM presents with a more insidious onset of symptoms, and it even has minimal or nonspecific symptoms at presentation, especially in patients with immunosuppression. The median duration of CM from the symptom onset to presentation is 6-12 weeks in non-HIV cases[22]. Therefore, the dichotomized variable of 10-30 days can help diagnose TBM more specifically and accurately.

CSF laboratory data are a vital part of the diagnosis of CNS infections. Similar to previous observations, patients with TBM were more likely to show features of high protein[15, 19, 23-25], and hyponatremia (the manifestation in CSF was a decrease in chloride concentration)[13, 17, 26]. We focus on the differences between this score and previous TBM score studies. Most of the previous studies[14, 15, 17, 19, 21] only limited the CSF leukocyte count in TBM to a cut-off value (>10-20*10^6/ml) rather than a range, which was of little significance for the differential diagnosis of confusing CNS infection, especially between TBM and BM. The reference range of CSF leukocyte count was limited to 100-500*10^6/ml in our study, which may more reasonable than that in the other prior scoring model settings. However, it was worth noting that CSF leukocyte count and classification as well as CSF biochemistry should be combined to have greater reference significance.

The unique element of our TBM scoring system is the proportion of CSF neutrophils and not the predominance of lymphocytes. Before treatment, the typical CSF cytology in TBM is characterized as a mixed cellular response with neutrophils, monocytes, and lymphocytes. Specifically, 47% of the patients had more than 50% neutrophils and 66.4% of the patients had more than 40% neutrophils. Using a cut-off value for a neutrophil proportion of 20%-75%, the sensitivity and specificity were 75.5% and 86.7%, respectively, with an AUC of 0.885. VM most commonly presents with a CSF lymphocytic predominance and rare neutrophils, and acute BM commonly presents with neutrophilic pleocytosis in the CSF (usually more than 80% before treatment), while CM usually presents with a mixed cell response pattern.
dominated by lymphocytes. The neutrophil proportion is overwhelmingly the strongest diagnosis predictor of TBM, therefore, weighting this component of the TBM score more than others is justified. It was worth noting that the application of the neutrophils proportion in the diagnosis of TBM was not consistent in previous studies. Based on cytological examination of CSF, several studies point out that in the acute phase of untreated TBM, the increase in the proportion of neutrophils was the early characteristic, which can exceed 50%, and in the subacute phase, whether effective treated or not, it changes into a mixed cytological reaction[27-31]. Recently, there are few studies on the CSF cytology of the TBM series. Some studies only put forward that CSF lymphocyte predominance (> 50%) was the characteristic manifestation of TBM, but did not classify the cells in detail[21, 23, 24]. Therefore, the reasons for the inconsistencies may be due to differences in the methodology used for CSF classification. Since the cellular component of CSF obtained from the lumbar area is generally scant, and considering the potential for cell loss, the clarity of cellular detail and the spectrum of stains offered, cytological examination of CSF has effectively addressed these aspects, ensuring the integrity of cell collection and the accuracy of classification[32]. Among all studies of this type, CSF cytology plays a central, indispensable role. Therefore, the score of lymphocyte > 50% in the expert consensus remains to be further studied and confirmed on a large scale.

TBM has several mechanisms to raise CSF neutrophils. The central pathogenesis of TBM has been widely believed to be the basal inflammatory exudate[33, 34]. Pathological studies found that early TBM without anti-tuberculosis treatment was exudative inflammation, and the inflammatory changes were mainly located at the basicranial with a large number of neutrophils[33]. Moreover, there were consistent reports that the earliest immune response during mycobacterial infection was a migration of neutrophils to the site of infection[35-37], with neutrophils having functions of phagocytosis, chemotaxis and killing pathogenic bacteria[38, 39]. Thus, an increase in neutrophils was first seen in CSF of TBM, and a subsequent mixed cytological response was seen in CSF cytology due to the chemotactic effect of neutrophils on other immune cells.

Imaging outcomes of CNS including meningeal enhancement and brain parenchyma nodules (tuberculomas) were independent predictors of TBM diagnosis, which was consistent with previous studies[21, 40-43]. In contrast to several reports which demonstrated hydrocephalus among the patients with TBM[41-43], this study failed to identify this parameter as a suitable parameter to distinguish TBM from other causes of meningitis. The reason may be that the pathological process of this study cohort was in the early stage of onset, and the disease did not develop to hydrocephalus. Of note, among the patients who underwent spinal cord imaging, 18 patients of TBM had spinal meningeal enhancement features, which were less common in the non-TBM group (2-5 cases). Considering that not all patients included in this study routinely undergo spinal cord MRI, this index was not included in the scoring system. However, the incidence of spinal meningeal enhancement in TBM should not be ignored. Gupta et al. reported that 46.4% (30/71) of TBM cases showed spinal involvement [44]. And Rohlwink et al. described spinal cord disease associated with TBM in a large pediatric cohort, and enhancement of the cord was present in over 70% of patients[45]. The mechanism of spinal involvement was considered to be related to M. tuberculosis hematogenous spread to the spinal cord or infiltration of the tuberculous
exudate into the lumbosacral region[46]. Recently, Liu, Y et al. [47] found that spinal involvement of TBM might be significantly associated with paradoxical reactions[48]. Our study suggests that extended contrast-enhanced spinal cord MRI should be performed as part of the assessment of TBM in patients with particularly high or progressively increased CSF protein content and/or symptoms involving the spinal cord, such as paraparesis, hemiparesis, paresthesia in lower limbs, sphincter dysfunction, and sensory loss.

Several limitations of this study should be acknowledged. First, this was a retrospective study, and data for some of the variables were inaccessible and could not be introduced into the logistic regression analysis. As a result, 104 patients were excluded due to insufficient data. Second, the TBM score model included only the risk factors available at the time of admission. However, changes in biomarkers measured repeatedly during the disease duration may provide important information in the whole process of TBM development. Additional studies might improve the accuracy of the score by updating the risk score, such as dynamic changes in CSF parameters and neuroimages. Third, the data in the present study were derived from the Chinese setting. The model needs to be tested prospectively at multiple centers to substantiate its broad applicability.

**Conclusions**

In conclusion, we provide a diagnostic scoring system validated in our population of patients, which predicts TBM at admission. This scoring system improves the accuracy of prediction and is easy to use clinically. Further research can examine the effect of the score on clinical decision making.

**Abbreviations**

TBM: tuberculous meningitis; VM: viral meningitis; BM: bacterial meningitis; CM: cryptococcal meningitis; CSF: cerebrospinal fluid; ROC: receiver operating characteristic curve; HIV: Human immunodeficiency virus; WHO: World Health Organization; CNS: central nervous system; MRI: magnetic resonance imaging; ANOVA: analysis of variance; AUC: areas under the curve; PCR: polymerase chain reaction; OR: odds ratio; GCS: Glasgow scale; TB: Tuberculosis; CT: computed tomography; AFB: acid-fast bacilli; NAAT: nucleic acid amplification test; CI: confidence interval.

**Declarations**

**Ethics approval and consent to participate**

Ethical approval was obtained from the Institutional Ethical Committee of the Third Xiangya Hospital, Central South University. No consent from patients was required. Data was anonymised prior to use and analysis.

**Consent for publication**
Not applicable.

**Availability of data and materials**

All data generated or analyzed during this study are included in this published article.

**Competing interests**

The authors declare that they have no competing interests.

**Funding**

This work was supported by the Youth Program of the National Natural Science Foundation of China (81801295). The funding plays a role in data collection.

**Authors' contributions**

Yuying LU and Chen Zhang collected and analyzed the patient data, and was a major contributor in writing the manuscript. Ru CHEN and Ding LIU analyzed the patient data, and was a major contributor in reviewing the manuscript. Zhongyang HU, Guang YAO, Huan YAO, and Qinghua ZHANG collected patient data. Zhen WANG and Zhi SONG interpreted the patient data. All authors read and approved the final manuscript.

**Acknowledgments**

We acknowledge the patients and their families, and the staff at the Third Xiangya Hospital, Central South University, and Changsha Central Hospital, as well as members of the laboratory of the Department of Neurology, the Third Xiangya Hospital, Central South University.

**References**


Table 1: Comparison of clinical features of patients with tuberculous meningitis and non-tuberculous meningitis at initial admission
<table>
<thead>
<tr>
<th>History and clinical criteria</th>
<th>TBM</th>
<th>Non-TBM</th>
<th>P-valuea</th>
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<tbody>
<tr>
<td><strong>VM</strong></td>
<td></td>
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<td><strong>CM</strong></td>
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<tr>
<td><strong>BM</strong></td>
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<tr>
<td><strong>n =113</strong></td>
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<tr>
<td><strong>n = 143</strong></td>
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<tr>
<td><strong>n = 61</strong></td>
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<tr>
<td><strong>n = 65</strong></td>
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</tr>
<tr>
<td><strong>Age</strong></td>
<td>39.03±17.17</td>
<td>39.31±17.31</td>
<td>50.83±15.95</td>
</tr>
<tr>
<td><strong>Gender (female)</strong></td>
<td>59(52.21%)</td>
<td>57(39.86%)</td>
<td>23 (37.70%)</td>
</tr>
<tr>
<td><strong>Symptom duration</strong></td>
<td>25.01±30.40</td>
<td>9.29±10.22</td>
<td>45.71±63.52</td>
</tr>
<tr>
<td><strong>Systemic symptomsb</strong></td>
<td>18 (15.93%)</td>
<td>1 (0.70%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Convulsion</strong></td>
<td>6 (5.31%)</td>
<td>10 (6.99%)</td>
<td>1 (1.54%)</td>
</tr>
<tr>
<td><strong>Mental disorder</strong></td>
<td>11 (9.73%)</td>
<td>16 (11.19%)</td>
<td>6 (9.23%)</td>
</tr>
<tr>
<td><strong>Altered consciousness</strong></td>
<td>37 (32.74%)</td>
<td>31 (21.68%)</td>
<td>11 (16.92%)</td>
</tr>
<tr>
<td><strong>GCS</strong></td>
<td>14.07±1.72</td>
<td>14.42±1.55</td>
<td>14.38±1.75</td>
</tr>
<tr>
<td><strong>History of tuberculosis</strong></td>
<td>28 (24.78%)</td>
<td>4 (2.08%)</td>
<td>11 (16.92%)</td>
</tr>
<tr>
<td><strong>Cranial nerve palsies</strong></td>
<td>11 (9.73%)</td>
<td>5 (3.50%)</td>
<td>12 (18.46%)</td>
</tr>
<tr>
<td><strong>Focal neurological deficit</strong></td>
<td>12 (10.62%)</td>
<td>12 (8.39%)</td>
<td>11 (16.92%)</td>
</tr>
<tr>
<td><strong>Laboratory data</strong></td>
<td></td>
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<tr>
<td><strong>CSF leukocyte count (106/ml)</strong></td>
<td>270.53±254.41</td>
<td>138.87±189.67</td>
<td>152.57±556.70</td>
</tr>
<tr>
<td><strong>CSF neutrophil proportion (%)</strong></td>
<td>43.92±19.48</td>
<td>4.81±11.21</td>
<td>22.85±21.55</td>
</tr>
<tr>
<td><strong>CSF protein (g/ L)</strong></td>
<td>1601.73±1008.08</td>
<td>714.29±423.29</td>
<td>902.95±650.28</td>
</tr>
<tr>
<td><strong>CSF sugar (mmol/ L)</strong></td>
<td>2.49±1.46</td>
<td>3.42±0.81</td>
<td>2.24±1.50</td>
</tr>
<tr>
<td><strong>CSF chlorine (mmol/ L)</strong></td>
<td>112.95±8.61</td>
<td>122.43±5.42</td>
<td>120.03±7.44</td>
</tr>
<tr>
<td><strong>Blood leukocyte count (109/ L)</strong></td>
<td>8.45±3.28</td>
<td>8.15±3.02</td>
<td>8.64±4.08</td>
</tr>
<tr>
<td><strong>Serum sodium (mmol/ L)</strong></td>
<td>133.46±5.92</td>
<td>137.59±4.51</td>
<td>137.02±6.12</td>
</tr>
<tr>
<td><strong>Serum sugar (mmol/L)</strong></td>
<td>6.11±1.44</td>
<td>5.20±1.09</td>
<td>6.36±2.76</td>
</tr>
<tr>
<td><strong>CNS imaging criteria</strong></td>
<td></td>
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<tr>
<td><strong>Hydrocephalus</strong></td>
<td>17 (15.04%)</td>
<td>0 (0.00%)</td>
<td>8 (12.31%)</td>
</tr>
<tr>
<td><strong>Meningeal enhancement</strong></td>
<td>76 (67.25%)</td>
<td>39 (27.27%)</td>
<td>24 (36.92%)</td>
</tr>
<tr>
<td><strong>Brain parenchyma nodulesc</strong></td>
<td>36 (31.86%)</td>
<td>0 (0.00%)</td>
<td>3 (4.62%)</td>
</tr>
<tr>
<td><strong>Cerebral infarction</strong></td>
<td>5 (4.42%)</td>
<td>0 (0.00%)</td>
<td>1 (1.54%)</td>
</tr>
<tr>
<td><strong>Spinal meningeal enhancementd</strong></td>
<td>18 (72.00%)</td>
<td>5 (55.55%)</td>
<td>2 (40.00%)</td>
</tr>
<tr>
<td><strong>Pre-contrast basal hyperdensity</strong></td>
<td>7 (6.19%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td><strong>Evidence of tuberculosis elsewhere</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chest radiograph suggestive of active tuberculosis</strong></td>
<td>36 (29%)</td>
<td>1 (0.70%)</td>
<td>13 (20.00%)</td>
</tr>
</tbody>
</table>

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CT/ MRI/ ultrasound evidence for TB outside the CNS 42 (37.17%) 1 (0.70%) 13 (20.00%) 3 (4.92%) 0.000
AFB identified or Mycobacterium tuberculosis cultured from another source 4 (3.45%) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0.000
Positive commercial M tuberculosis NAAT from extra-neural specimen 10 (8.85) 0 (0.00%) 0 (0.00%) 0 (0.00%) 0.022

TBM = tuberculous meningitis; VM=viral meningitis; BM=Bacterial meningitis; CM=Cryptococcal meningitis; GCS=Glasgow scale; TB = tuberculosis; CSF = cerebrospinal fluid; CT = computed tomography; MRI = magnetic resonance imaging; CNS=Central nervous system; AFB=acid-fast bacilli; NAAT=nucleic acid amplification test.

Table 2: Logistic regression results and indices of the scoring system for the diagnosis of tuberculous meningitis

<table>
<thead>
<tr>
<th>History and clinical criteria</th>
<th>β-coefficient</th>
<th>P-value</th>
<th>odds ratio (95%CI)</th>
<th>Diagnostic score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration: 10–30 days</td>
<td>1.603</td>
<td>0.000</td>
<td>4.967(2.362-10.444)</td>
<td>1</td>
</tr>
<tr>
<td>Systemic symptoms(^a)</td>
<td>1.868</td>
<td>0.040</td>
<td>6.478(1.089-38.525)</td>
<td>1</td>
</tr>
<tr>
<td>Evidence of tuberculosis elsewhere outside CNS</td>
<td>1.131</td>
<td>0.019</td>
<td>3.099(1.204-7.973)</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF leukocyte count: 100-500*106/ml</td>
<td>0.616</td>
<td>0.046</td>
<td>1.852(0.925-3.706)</td>
<td>1</td>
</tr>
<tr>
<td>CSF proportion of neutrophils: 20%-75%</td>
<td>2.331</td>
<td>0.000</td>
<td>10.289(5.132-20.626)</td>
<td>2</td>
</tr>
<tr>
<td>CSF protein: &gt;1 g/L</td>
<td>1.403</td>
<td>0.000</td>
<td>4.068(1.987-8.328)</td>
<td>1</td>
</tr>
<tr>
<td>Serum sodium &lt;137 mmol/l</td>
<td>1.408</td>
<td>0.000</td>
<td>4.967(1.948-8.568)</td>
<td>1</td>
</tr>
<tr>
<td>Cerebral imaging criteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningeal enhancement</td>
<td>0.625</td>
<td>0.048</td>
<td>1.869(0.897-3.891)</td>
<td>1</td>
</tr>
<tr>
<td>Brain parenchyma nodules(^b)</td>
<td>1.373</td>
<td>0.014</td>
<td>3.946(1.320-11.974)</td>
<td>1</td>
</tr>
</tbody>
</table>

CSF = cerebrospinal fluid; OR = odds ratio; CI = confidence interval.

\(^a\) P-value refers to the comparison among TBM, VM, BM, and CM; \(^b\) Systemic symptoms were defined as one or more of the following: low fever, weight loss, night sweats, or persistent cough coughing for more than 2 weeks[21]; \(^c\) Brain parenchyma nodule were defined as discrete or coalescing cerebral masses showing nodular or ring-shaped enhancement\[47\]; \(^d\) Data shown as a proportion of patients who had spinal imaging.
Figure 1

Receiver-operating characteristic (ROC) curve of the study cohort
Figure 2

Receiver-operating characteristic (ROC) curve of the validation cohort

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1.docx
- AdditionalFile2.docx